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Regulation of Dietary Supplements in the United States: Understanding the Dietary Supplement Health and Education Act

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One of the most perplexing pieces of legislation to impact the practice of the healing arts in the United States is the Dietary Supplement Health and Education Act (DSHEA). The act, passed by Congress on October 15, 1994 and signed into law October 25, 1994 by President Bill Clinton, would change the practice of medicine in the US. At the time of its passage, only approximately one-third of the public had used dietary supplements. Today, less than one decade later, approximately 80% of Americans have tried or are using dietary supplements. In passing this landmark legislation, Congress was intent on "improving the health status of United States citizens [which] ranks at the top of the national priorities of the Federal government."[1–4]

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Definition of Dietary Supplement

For the first time, dietary supplements were defined by law. According to the act, the term "dietary supplement" means a product (other than tobacco) that is intended to supplement the diet containing one or more of the dietary ingredients listed here: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary supplement used by humans to supplement the diet by increasing the total dietary intake; or a concentrate, me-

tabolite, constituent, extract, or combination of any ingredient described here.[1,2] Although botanicals are specifically mentioned in DSHEA, these ingredients may be used not only in dietary supplement products but also as drugs, biologics, and devices, depending on their intended use.

The form of the product is an integral part of the definition. Dietary supplements must be products that can be ingested in forms such as capsules, powders, softgels, gelcaps, tablets, or liquids. Products that are represented as "conventional foods," such as beverages, gums, spreads (eg, margarine), or any item that is a sole item of a meal or diet cannot be dietary supplements. Thus, soups or potato chips or beverages containing herbal ingredients, such as ginseng or St. John's wort, are not considered dietary supplements.

Labeling Requirements

In the US, foods, drugs, devices and biologics (vaccines) are regulated by their intended use. Intended use is determined by the product's labeling. Labeling includes not only the actual label and the claims made on the product bottle, package, or package insert but also all other materials accompanying the product, such as advertising and promotional materials, including broadcast and print advertisements, catalogs, infomercials, and direct marketing materials. Such labeling is required to be "truthful and not misleading."

From the passage of DSHEA in 1994 until March 1999, when the new regulations became enacted, no labeling regulations existed for dietary supplements. This resulted in products that bore varied amounts and quality of information, or lack thereof, on the label. Dietary supplements must now meet the new requirements. Labels must identify the product as a "dietary supplement." According to the Nutrition Education and Labeling Act of 1990, which defines the requirements for the Food Label, dietary supplements were required to provide information about the nutritional value of the product in a box called "Supplement Facts." The name and quantity of each ingredient or, in the case of a proprietary blend, the "total quantity of all ingredients in the blend" must be listed. In addition, the quality of each ingredient must be stated. If a dietary supplement claims to contain ingredients that conform to the standards of a particular compendium, such as the United States Pharmacopeia, it must conform to those requirements. The Food, Drug, and Cosmetic Act identifies official compendiums, such as the United States Pharmacopeia and the Food Chemicals Codex. Finally, manufacturers must have substantiation for claims made about the product (see later) and must notify the Food and Drug Administration (FDA) within 30 days after first marketing a product with a statement of nutritional support that such a statement is being made. Because these statements are not reviewed by the FDA before marketing, this disclaimer must be made: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Failure to comply with the labeling regulations results in a product being "misbranded."[5,6]

Two regulatory agencies have authority over product labeling. Prescription products are under the purview of the FDA, both the label and the "labeling." For nonprescription products, such as over-the-counter drugs, foods (including dietary supplements), and cosmetics, the Federal Trade Commission has the oversight for the advertising and promotion, whereas the FDA is responsible for the product labels.

Third-Party Literature

To inform the public about dietary supplements, Congress allowed retailers and distributors to display "third-party" literature (information not published directly by the manufacturer) where dietary supplements are sold. However, the information must be

in a location not physically next to the products. To do this, DSHEA states that under certain conditions, this information "shall not be defined as labeling when used in connection with the sale of a dietary supplement." More importantly, third-party literature cannot promote a particular manufacturer or brand of dietary supplement. The kinds of information permitted include articles, book chapters, and official abstracts of peer-reviewed scientific publications. Third-party literature used in connection with the sale of dietary supplements must be truthful and not misleading and present a balanced view of the available scientific information. These documents must be reprinted in their entirety and cannot be reformatted to include or exclude information, nor may promotional product literature be appended.[1,8]

Quality Controls and Manufacturing

The use of dietary supplements has been plagued by concerns regarding product quality. Consumer Laboratories, which is performing comparison studies on single-ingredient dietary supplements, has drawn attention to the fact that there is a wide range of variability in the quality of manufacturing for products marketed in the US. Some products contain too little, others contain too much of an ingredient. Still, others may not even contain the correct ingredient or the correct form of the ingredient. DSHEA authorized the FDA to establish Good Manufacturing Practices for dietary supplements. Good Manufacturing Practices require specific standards be met for facilities, record keeping, and sourcing of ingredients. In February 1997, the FDA published a notice stating its intention to develop Good Manufacturing Practices regulations. After receiving public comments, and based on many meetings and working groups, which included industry representatives, the agency has written final regulations that are awaiting final approval. Until the regulations are in place, supplements are required to meet the minimal manufacturing requirements for foods. Good Manufacturing Practices for foods are mostly concerned with tolerances for filth, pesticides, and other contaminants, whereas Good Manufacturing Practices for drugs are concerned with stability, potency, and lot-to-lot consistency. Dietary supplement Good Manufacturing Practices for dietary supplements will be more rigorous than those for foods, but not as stringent as those for drugs.[9,10]

Because dietary supplements are sold directly to the public, they are often confused with nonprescription or over-the-counter drugs. However, over-the-counter drugs are manufactured according to the same standards as prescription drugs, under conditions that are monitored by FDA's direct oversight.

Dietary Supplement Claims

DSHEA authorized five types of claims that are permissible on dietary supplements: nutritional claims, claims of well-being, health claims, nutrient content claims, and claims that the supplement affects the structure or function of the body.[1,2]

Nutritional claims relate a product's benefit to a classical nutrient deficiency. These claims are made for the essential vitamins and minerals. Although these claims do not require preapproval by the FDA, to be valid, the claim must disclose the prevalence of the deficiency or disease in the US that the nutrient is meant to prevent. Examples include "vitamin C prevents scurvy" and "iron prevents iron-deficiency anemia."

Claims of well-being describe effects on general well-being from consumption of a nutrient or dietary ingredient. These claims are simply statements of well-being, such as "makes you feel happy" or "helps you relax" or feel "more energetic." These claims do not require preapproval by the FDA.

Health claims characterize the relationship between a nutrient in the food to a disease or health-related condition. As such, these claims are the closest to the "disease"

claims that are reserved for drug products. Health claims are usually couched in the context of disease prevention "to reduce the risk of developing some cancers when taken in the context of a complete diet." Health claims were originally authorized for foods under the Nutrition Education and Labeling Act of 1990. In 1994, DSHEA amended the law to authorize health claims on dietary supplement products. These claims require preclinical (in vitro and animal) and clinical (human trial) data for support. Unlike other categories of claims that can be made for dietary supplements, health claims must be approved by the FDA before the product is marketed.[11,12]

Nutrient content claims describe the level of a nutrient or dietary substance in the product, using relative terms such as "good source of fiber," "high in vitamin C," or "fat-free." Nutrient content claims may be made only if the FDA has a regulation specifying the criteria that a food must meet to use the claim. With few exceptions, nutrient content claims can be made only for nutrients or dietary substances that have an established daily value. The requirements that govern the use of nutrient content claims help ensure that descriptive terms such as "high" or "low" are used consistently for all types of food products and are thus meaningful to consumers.[11]

Structure or function claims describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the human body, or characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function. Structure or function claims were first authorized by DSHEA and are the most contentious and confusing of the dietary supplement claims. Before the passage of DSHEA, structure or function claims would have been "disease" (or "drug") claims requiring review and approval by the FDA before marketing the product. The Food, Drug, and Cosmetic Act defines "drugs" as "articles that are intended to diagnose, prevent, treat, mitigate, or cure a disease" and that "affect the structure of function of the body." DSHEA amended the law to permit a product meeting the definition of a dietary supplement to make structure or function claims without being a drug, as long as the claims were "truthful and not misleading."

On January 6, 2000, 5 years after the passage of DSHEA, the FDA published its final regulations on structure or function claims by specifying criteria as to what they are not: "disease claims" (Table 2). In its deliberations, the FDA was concerned that allowing disease claims would encourage consumers to self-medicate. Without proven benefits, dietary supplements might be used to treat or prevent disease, resulting in someone foregoing or delaying effective treatment for serious and life-threatening conditions.[13,14]

Regulations published in draft by the

TABLE 1. Regulation of Foods and Drugs in the United States

Drugs	Dietary Supplements
Rigorous manufacturing controls concerned with purity, potency, stability, lot-to-lot consistency	Manufacturing controls concerned with identity, filth
Approved for safety and efficacy	Not approved for safety or efficacy
For particular "intended use"	For the general public to use whenever
Disease claims "to diagnose, treat, mitigate, cure, or prevent"	Claims: nutritional, nutrient content, "well-being", health, structure or function
Not generally recognized as safe, unless proven to be safe in adequate and well-controlled clinical trials	Many ingredients are "generally recognized as safe"
Burden of proof of safety on the manufacturer	Burden of proof of safety on Food and Drug Administration
New products are developed under INDs and approved based on premarket new drug applications (NDAs)	No premarket approvals except for health claims

TABLE 2. FDA Criteria for Determining When a Statement Is a Disease Claim

1. Has an effect on a specific disease or class of diseases
2. Has an effect, using scientific or lay terminology, on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of different specific diseases
3. Has an effect on an abnormal condition associated with a natural state or process, if the abnormal condition is uncommon or can cause significant or permanent harm
4. Has an effect on disease through one or more of these factors:
   a. Name of the product
   b. Statement about the formulation of the product, including a claim that the product contains an ingredient that has been regulated by the Food and Drug Administration as a drug and is well know to consumers for its use in preventing or treating a disease
   c. Citation of a publication or reference, if the citation refers to a disease use
   d. Use of the term "disease" or "diseased"
   e. Use of pictures, vignettes, symbols, or other means
5. Belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease (eg, antiviral)
6. Is a substitute for a product that is a therapy for a disease
7. Augments a particular therapy or drug action
8. Has a role in the body's response to a disease or to a vector of disease
9. Treats, prevents, or mitigates adverse events associated with a therapy for a disease and if the adverse events constitute
10. Otherwise suggests an effect on a disease or diseases

From: Title 21 Code of Federal Regulations, Section Sec. 101.93 Certain types of statements for dietary supplements.

The regulations defined criteria for determining when a statement about a dietary supplement is a disease (or "drug") claim requiring previous approval as a drug or previous authorization as a health claim. A statement about a dietary supplement will be considered to be a disease claim if it explicitly or implicitly claims that the product has at least one of characteristics in this Table.

FDA in April 1998 drew more than 250,000 comments. To finalize its position, the FDA held several stakeholders meetings representing: state and federal agencies; conventional food, dietary supplement, and pharmaceutical industries; consumer and patient groups; health professionals; the public health community; and the insurance industry. On August 4, 1999, the last stakeholders meeting took place in Washington, DC to address remaining controversies. One of the more contentious issues was the definition for "disease" in the FDA's proposed regulations. The draft had defined disease as "a characteristic set of signs or symptoms recognizable to health care professionals or consumers . . . as an abnormality." This definition, however, differed from the narrower definition the agency had used earlier in promulgating the regulations for the Nutrition Education and Labeling Act, thus raising objections from the food industry. Because disease claims are reserved for drugs, and dietary supplements could not make disease claims, the definition affected how the FDA would handle products intended to treat abnormal conditions associated with naturally occurring life stages, such as aging, menopause, pregnancy, and the menstrual cycle. Because these conditions are not diseases, they could be associated with abnormal conditions. At the meeting, health professional groups, such the American Urological Association, the National Organization for Rare Diseases, and the American Public Health Association, were asked to comment on the debate. Although invited, the American College of Obstetrics and Gynecology decided not to participate. Based on this meeting and public comments, the FDA crafted its position that became part of the final regulations. The final regulations expanded the number of acceptable structure or function claims, many of which affected conditions experienced by women. In particular, the definition of "disease" was narrowed to exclude common gynecologic conditions. This effectively allowed dietary supplements to be promoted and advertised for hot flashes, symptoms surrounding the menstrual cycle and menopause, and morning sickness and edema in pregnancy.

Almost as soon as they were published, the new regulations were met with angry

objections from consumers and the health community. The irony of allowing the marketing of dietary supplements for morning sickness would later be highlighted at a public advisory meeting that was called by the FDA in March 2000 to reexamine the structure or function claims concerning conditions of pregnancy. One of the major events that had shaped the agency's law and regulatory authority was the thalidomide disaster of the early 1960s. Marketed in Europe after minimal scrutiny, thalidomide, a drug indicated for the treatment of nausea and vomiting during pregnancy, had been touted as a "safer alternative" to then-current treatments, primarily barbiturates. Although the drug never made it to the US market, saving millions of babies from the devastating phocomelia experienced by children whose mothers used the drug, Congress swiftly passed the Kefauver–Harris amendments of 1962 to prevent such a tragedy by significantly tightening the regulatory process for US drugs. Now, manufacturers had to show that a drug was not only safe but also efficacious for its intended use before approval for marketing in the US.

At the March meeting, many groups spoke out for change in the regulations. Trade groups, such as the Consumer Healthcare Products Association and the Council for Responsible Nutrition, representing both the over-the-counter drug and dietary supplement industries, encouraged their members to refrain voluntarily from needlessly marketing their products to pregnant women and had already recommended a product warning label for dietary supplements similar to the wording used on over-the-counter drugs. In May 2000, the Consumer Healthcare Products Association filed a petition with the FDA proposing this labeling statement for supplements with insufficient data supporting their safe use: "If you are pregnant or nursing a baby, ask a health care professional."

Safety and Efficacy, Risk and Benefit

Before marketing, both the risks and benefits of a drug must be carefully investigated and documented through the evaluation of safety and efficacy testing in "adequate and well-controlled trials." Marketing is permitted only when the agency concludes that the documented benefits of the drug outweigh any known and potential risks. A drug that has significant risks may be approved, but it will be sold only under a prescription legend to ensure that it is essential for treatment and that health professionals will manage the risks. The benefit-to-risk ratio is assessed even for over-the-counter drugs. No comparable testing and approval process is in place for dietary supplements. Although the manufacturer must have substantiation for a structure or function claim, this documentation is not reviewed by the FDA before the product is marketed.

Although not approved for safety or efficacy, a dietary supplement is considered to be adulterated if there is inadequate information to provide reasonable assurance that its ingredients do not present a "significant or unreasonable risk" of illness or injury. Dietary supplements may contain either known ingredients in the food supply that are "generally recognized as safe" (GRAS) or "new dietary ingredients," for which safety must be confirmed. Any ingredient not currently "generally recognized as safe," but one that has been in the food supply in the US before October 15, 1994, can be considered a "new dietary ingredient." DSHEA requires a supplement manufacturer to notify the FDA at least 75 days before marketing products containing new dietary ingredients. This notification must include sufficient information to document the safety of the dietary ingredient.[15,16] Any interested party, including a manufacturer of a dietary supplement, may petition the FDA to issue an order prescribing the conditions of use under which a new dietary ingredient will reasonably be expected to be safe. However,

in passing DSHEA, Congress transferred the burden of proof from the manufacturer to the federal government to show that a dietary supplement is unsafe.

Reporting Adverse Events

To satisfy the burden of proof, a causal relationship is sought between ingestion of a dietary supplement and an adverse event (AE). Because supplements often have multiple ingredients, and because most consumers use multiple supplements and combine them with over-the-counter and prescription drugs, establishing a causal relationship between a particular ingredient and a type of AE is usually impossible based on the passive reporting systems in place. In addition, consumers using dietary supplements equate safety with terms such as "natural," and thus fail to consider supplements as a cause of their problem. Finally, because supplements are sold directly to the public and sales cannot be tracked, the total number of doses sold annually is unobtainable. To determine the incidence of AEs, the number of events must be divided by the total number of doses administered. Obviously, the calculation cannot be computed if the denominator is unknown.

Although food manufacturers, including those making dietary supplements, are not legally required to report AEs from their products, the FDA encourages such reporting. In 1993, as part of its revised agency-wide MedWatch program for adverse event reporting, the FDA established the Special Nutritionals Adverse Event Monitoring System (SNAEMS) to track the AEs reported to the FDA from dietary supplements and other special nutritional products. The FDA Center for Food Safety and Applied Nutrition maintains SNAEMS or MedWatch database. Data entered into the SNAEMS database may be accessed by the public at the agency's website (www.fda.gov).

Role of the Physician

Physicians can take a proactive role by inquiring about the use of dietary supplements in their patients. Results of surveys have shown that only a minority of patients willingly offer this kind of information to their physicians. Commonly, supplement ingredients, such as ginseng, willow bark, vitamin E, and many others, are known to alter platelet and coagulation factor function. Products such as ephedra (also known as Ma Huang), gingko, and kava kava can adversely affect cardiovascular or neurologic function. Patients undergoing surgical procedures for which anesthesia is required should be cautioned against using any unnecessary dietary supplements before or shortly after the procedure.

Thus, physicians need to become knowledgeable about the possible benefits and adverse effects of dietary supplements. This goal is not as simple as it may appear. Quality information on the effects of dietary supplements is scattered and not always easy to determine. The number of journals available today has proliferated, and many with mainstream-sounding titles are not scientifically grounded. Even the term "peer-reviewed" may hold a wide range of interpretations. Because research funding has become more difficult to obtain, authors should be scrutinized for potential conflicts of interest and bias in their reporting. Also, books and Internet sites rely heavily on First Amendment rights. Most are not vetted and are often hosted by those with monetary interest in the product, such as manufacturers or distributors. Those from recognized institutions and sources are generally the most balanced resources, particularly those in which the peer-review process is established and transparent. Academic and government websites are critically reviewed and not subject to bias in the same way as those maintained by product retailers. At the National Institutes of Health, the Office of Dietary Supplements, established under DSHEA, is charged with developing and maintaining a

database for dietary supplement research and for sponsoring scientific research studying the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions. The National Institutes of Health is planning a conference for January 2002 that will further investigate the use of dietary supplements by women of reproductive age (www.nih.gov).

Safety and efficacy data may also be elusive. The better studies on a particular product may be published in a foreign language, because many of the ingredients used in dietary supplements are marketed as drugs outside the US. Not only does US law not demand that dietary supplement manufacturers study their products in the same way that drug manufacturers must, but the commodity nature of dietary ingredients in the US in the absence of composition patents provides no incentive for the manufacturer to conduct such research. For these reasons, little may be known about the long-term effects, toxicity, or interactions in combination with other products, particularly prescription drugs.

Therefore, patients requiring prescription medication should avoid using dietary supplements, unless there is sufficient information regarding the effects of the supplements on the pharmacokinetics and pharmacodynamics of the drug. In addition, because little is known about the reproductive toxicity of most supplements, women of childbearing age or those who are pregnant or lactating should be cautioned against using any product that has not been shown to be both safe and necessary. When the rationale does exist to recommend a dietary supplement, health care professionals should assist the patient in locating dietary supplements manufactured by reputable manufacturers. The physician should contact the manufacturer to find out what kinds of quality control are being used and should demand that data be sent to him or her.

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